UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,958	09/15/2005	Barbara Ensoli	11340-007-999	1299

20583 7590 10/02/2009

JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
KINSEY WHITE, NICOLE ERIN	
ART UNIT	PAPER NUMBER
1648	
MAIL DATE	DELIVERY MODE
10/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/549,958	ENSOLI, BARBARA	
	Examiner	Art Unit	
	NICOLE KINSEY WHITE	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *76-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/8/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 76-86 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Weichold et al (WO 00/33654).

The claims are drawn to a method for treating a tumor or blocking cell migration or invasion, comprising administering indinavir at a daily dose of 1200 mg to a human subject having a tumor or in need of said blocking.

Weichold et al. discloses using HIV protease inhibitors to treat diseases and conditions including cancer (see page 23, lines 22-25). Weichold et al. states that cancer patients, or persons at increased risk of developing cancer, will be administered at least one protease inhibitor to boost and/or modulate the immune system, thereby resulting in effective treatment and/or prophylaxis of cancers (see page 33, lines 7-17). Weichold et al. further states that such protease inhibitor can be used by itself or in conjunction with other anti-cancer treatments or prophylaxis, e.g., chemotherapeutics, radiation, other immune modulators, cytokines, and immunotherapeutics. Cancers that are treatable and/or preventable include breast, prostate, liver, bladder, lung,

esophageal, stomach, skin, pancreatic, brain, uterine, colon, brain, head and neck, and ovarian cancer (see page 33, lines 21-26).

The inhibitors of Weichold et al. include several known protease inhibitors (see page 25, line 3 to page 26, line 21). However, Weichold et al. specifically named and tested Ritonavir, Saquinavir, Indinavir, and Nelfinavir in various assays. Weichold et al. states that preferably a microbial or viral protease inhibitor, and more preferably HIV- 1 protease, proteasome, serine protease, or cysteine protease inhibitor can be used. Examples thereof include, e.g., Ritonavir, Saquinavir, Nelfinavir and Indinavir, MG132, lactacystin, or cytochrome P450 inhibitor (see page 22, lines 19-22). Weichold et al. found that the HIV protease inhibitor, Ritonavir, increased apoptotic death in immortalized (tumor) cells and inhibited tumor growth (see, for example, Figures 11, 21, 25 and 26). The HIV protease inhibitors can be administered orally, parenterally, topically or by inhalation. The term parenteral as used herein includes intravenous, intraperitoneal, intramuscular, subcutaneous, rectal or vaginal administration. The dosage is preferable 0.5 to 20 mg/kg per day for oral or parenteral administration (see page 29, lines 12-24). For a human with a mass of 75 kg, this translates to a range of 37.5 mg to 1500 mg of HIV protease inhibitor per day.

Weichold et al. found that HIV protease inhibitors have anti-inflammatory effects that influence endothelial cell activation and proliferation, thus inhibiting mechanisms that also can lead to tumor neovascularization (i.e., cell migration and invasion) (see page 71, lines 3-12 and Figures 15-18). In addition, Weichold et al. found that HIV protease inhibitors inhibited *in vitro* and *in vivo* tumor formation by Kaposi sarcoma (KS)

derived cells and leukemia-derived cells in immune deficient BNX-mice and in immune competent BALB\c mice (see Figures 27a-b), indicating that the anti-neoplastic effect of the HIV protease inhibitor is independent of tumor-specific immune responses (see page 76, lines 4-20).

With regard to the dose of 1200 mg/day, according to section 2144.05 of the MPEP, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.")

A particular parameter must first be recognized as a result-effective variable, i.e., a variable, which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). In the instant application, the dose range of Weichold et al. produced a recognized result (i.e., decreased tumor growth) and Weichold et al. teaches a range of about 37.5 mg to 1500 mg of HIV protease inhibitor per day (see above). Absent unexpected results, determining other optimum or workable dosages such as 1200 mg is routine experimentation.

With regard to Indinavir and Nelfinavir, Weichold et al. does not specifically teach administering a composition comprising both Indinavir and Nelfinavir. However, Weichold et al. does teach that each HIV protease inhibitor can be used to treat conditions such as cancer, tumors and neovascularization.

It would have been obvious to one of skill in the art to combine the indinavir and nelfinavir to treat cancer or tumors as taught by Weichold et al.

One of skill in the art would have been motivated to administer a combination of agents, such as indinavir and nelfinavir because both are useful for treating cancer or tumors as taught by Weichold et al., and one of ordinary skill in the art would have had a reasonable expectation of success that the combination treatment would result in the intended use of treating cancer or tumors. A multi-drug treatment approach to tumor therapy is expected to be more aggressive.

Further, the courts have said: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose . . . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). In this case, applicants are combining two known HIV protease inhibitors which are taught to be useful for treating cancer and/or tumors.

Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

In the reply dated June 6, 2009, applicant argues that the fact that it would not be obvious to use indinavir because indinavir and ritonavir have different profiles and work by different mechanisms. All of applicants' arguments have been fully considered but are not found persuasive.

The entire Weichold et al. reference teaches the use of protease inhibitors, in particular, HIV protease inhibitors, to treat cancer and tumors.

Weichold et al. states the following:

1. The present invention is directed toward the use of microbial or viral protease inhibitors or HIV-1 protease, proteasome, serine protease, or cysteine protease inhibitors in particular to treat diseases and conditions including cancer, autoimmune disorders, keratinization disorders . . . (see page 23, lines 22-25).

2. Another use of HIV-1 and other protease inhibitors is for the treatment of disorders involving T-cells such as T-cell related cancers . . . (see page 31, lines 20-23).

3. Protease inhibitor can be used by itself or in conjunction with other anti-cancer treatments or prophylaxis, e.g., chemotherapeutics, radiation, other immune modulators, cytokines, and immunotherapeutics. Cancers which should be treatable and/or preventable according to the invention include, by way of 25 example, breast,

prostate, liver, bladder, lung, esophageal, stomach, skin, pancreatic, brain, uterine, colon, brain, head and neck, and ovarian cancer (see page 33, lines 21-27).

4. The HIV protease inhibitors of the invention are also applicable in treating other diseases or conditions which occur or persist due to an impaired or compromised immune system. For example, cancers persist in hosts due to the immune system no longer recognizing antigens presented on the surface of tumor cells. Treatment in accordance with the invention, will enhance anti-cancer immune responses as mediated by HIV protease inhibitor-activated immune cells resulting in the restoration of immune surveillance (see page 37, line 23 to page 38, line 2).

5. In addition, HIV protease inhibitors can be used to alter cellular metabolism in cancer to make cancer cells less neoplastic and more accessible for "conventional" anti-cancer drugs and host cell cycle control (see page 38, lines 8-10).

Furthermore, there are several examples where the HIV protease inhibitor Ritonavir was used to treat cancer and tumors (see Examples and Figures, especially Figures 25 and 26).

Thus, Weichold et al. teaches the use of HIV protease inhibitors to treat cancer and tumors. Weichold et al. also teaches several protease inhibitors that can be used; however, Weichold et al. singles out four HIV protease inhibitors ritonavir, nelfinavir, indinavir and saquinavir. Further, HIV protease inhibitors in general are well known in the art. It would be reasonable for one of ordinary skill in the art, using the teachings of Weichold et al., to choose any of the known HIV protease inhibitors including ritonavir, nelfinavir, indinavir and saquinavir to treat cancer or tumors.

Applicant next argues that because Ritonavir and Indinavir have different mechanisms and one of ordinary skill in the art would not substitute Indinavir for Ritonavir. This argument is not found persuasive.

Footpad swelling (and the other conditions described by applicants) is very different compared to cancer. Accordingly, observations of the effects of the inhibitors on footpad swelling are not predictive of what may occur when treating cancer with the same inhibitors. As stated above, Weichold et al. specifically names Ritonavir, Saquinavir, Nelfinavir and Indinavir and performed assays using these specific HIV inhibitors, especially Ritonavir. Based on the observations of Weichold et al. (see, for example, Figures 2 and 3), where Ritonavir, Saquinavir, Nelfinavir and Indinavir provided protective effects for cells, one of ordinary skill in the art would find motivation to substitute any of the other named and tested HIV protease inhibitors (Saquinavir, Nelfinavir and Indinavir) for Ritonavir in the tumor assays and have a reasonable expectation of success and predictability because, as mentioned above, all four HIV inhibitors produced a similar result in prior assays (suggesting that they work via similar mechanisms). Furthermore, it would have been obvious to try Saquinavir, Nelfinavir and Indinavir in the Ritonavir-tumor assays with a reasonable expectation of success because there is a finite number of HIV protease inhibitors specifically suggested by Weichold et al.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NICOLE KINSEY WHITE whose telephone number is (571)272-9943. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nicole Kinsey White/
Examiner, Art Unit 1648

/Stacy B Chen/
Primary Examiner, Art Unit 1648